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Nutritional influences during the life course on the lean body mass of individuals in developing countries

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Abstract

Double burden of childhood under nutrition and adult onset adiposity in transitioning societies poses a significant public health challenge. Suboptimal lean body mass (LBM) development could partly explain the link between these two forms of malnutrition. The paper uses a life course approach to examine the evidence related to the role of nutrition in 'developmental programming' of LBM as well as the nutritional influences that impact the LBM throughout the life course. Studies from the developing countries assessing the relationship of early nutrition with later LBM provide important insights. Overall, the evidence is consistent suggesting a positive association of early nutritional status (indicated by birth weight and growth during first 2 years) with LBM in later life. Evidence on the impact of maternal nutrition supplementation during pregnancy on later LBM is inconsistent. In addition, the role of nutrients (protein, zinc, calcium, vitamin D) that can impact the LBM throughout life course is described. The paper argues that promoting optimal intakes of these important nutrients throughout life course would be important to reduce childhood under nutrition as well as improving the LBM of adults.

Key words

Lean body mass, body composition, muscle mass, nutrition, physical activity, Developmental programming

Introduction

As a result of epidemiological and nutrition transition, developing and middle-income countries are experiencing a rapid increase in non-communicable diseases (NCDs) including type 2 diabetes mellitus, hypertension, dyslipidemia and cardiovascular disease (CVD), all known to be associated with obesity. [1-3] However, the prevalence of obesity assessed using a body mass index (BMI) criterion, although increasing rapidly in recent years, is still low in these settings. In contrast, under nutrition, especially childhood under nutrition, is highly prevalent and is still a priority area. [4] In addition, studies from China, Brazil, Mexico and Russia have reported co-existence of under nutrition in children and over nutrition in adults living in the same household. [5,6] The double burden of under nutrition and obesity-related chronic diseases has been highlighted as a key concern in societies in transition.

A number of studies assessing the ethnic differences in body composition have highlighted the peculiar 'high fat low muscle mass' composition of South Asians compared to the other ethnic groups.[7-10] This particular body composition characteristic is considered an important determinant of the elevated risk of metabolic syndrome in this population. Studies of south Asians who migrated to western countries have also shown that they tend to have a lower lean body mass (LBM) and higher fat mass (FM) at a given BMI than other ethnic groups in spite of adopting the lifestyle of the residents of the host country. [11]

Evidence suggests that this fat phenotype in relatively thin individuals may be "programmed" by under nutrition in early life as the ethnic differences in body composition are evident even at birth. For example, a few studies, but not all, comparing the body composition of south Asian and European neonates have shown that south Asian babies had significantly lower LBM than European babies but their FM was relatively spared. [12-15] In addition, a large number of studies (mainly observational studies in humans and animal

experiments) conducted during the past two decades have indicated that compromised nutrition and growth during early life may be associated with subsequent lower LBM , adiposity and metabolic syndrome. [16-19]

Early nutritional influences, however, cannot completely account for the low LBM in some population groups and it is well recognized that nutritional influences operating during later life have cumulative impact on the adult LBM. A large body of evidence suggests that nutritional and exercise interventions help improvement of LBM throughout life course [20]. We have therefore examined the possible nutritional influences on adult LBM using a life course approach which emphasizes that influences affecting health and disease in adult life operate during different life stages cumulatively and interactively[21]. Life course approach proposes two theoretical models in which the exposures may affect the disease risk: a. 'Critical period' or 'developmental programming' model, and b. 'Accumulation of risks' as a result of long term gradual insults [22]. We have therefore reviewed two lines of evidence: 1. the role of early nutrition in developmental programming of LBM and 2. the role of nutritional influences that impact the LBM throughout life course (**Figure 1**). Collective assessment of these two lines of evidence provides important insights regarding the co-existence of double burden of childhood under nutrition and later adiposity in developing countries.

Evidence on the relationship between early nutrition and later LBM

Early evidence on the developmental programming of LBM was provided by studies indicating a positive relationship between birth weight and LBM in later life. This evidence is dominated by studies from developed countries as majority of these studies used historical records of birth weight and childhood growth as indicators of early nutrition and such records are extremely rare in developing countries. [23] With increased interest in this area, a number of

cohorts have been established in developing countries. These cohort studies have typically traced the participants of studies on child nutrition conducted in the past few decades and used records of their birth and growth information to assess the relationship of early nutrition with body composition and cardio-metabolic risk factors at a later age. Offspring body composition patterns in the developing country settings with persistent under nutrition through lifecycle may be different compared to those seen in developed countries where under nutrition in postnatal life is rare [24]. Therefore, for the purpose of this review, we have examined the studies from developing countries that assessed the relationship between early nutrition and later body composition.

Although a large number of studies have assessed the relation of early life influences on adult obesity using a proxy indicator of body mass index (BMI), BMI alone masks the relationship between early nutrition and the lean and the fat components of total body mass. [25] We have therefore restricted this review to studies that have assessed the LBM or muscle mass, a major component of LBM, as outcome.

Search strategy

The electronic databases MEDLINE was searched using the term "(fat-free mass OR lean body mass OR Body composition) AND (birth weight OR early childhood growth OR infant weight gain OR nutrition supplementation in pregnancy OR maternal nutrition OR maternal diet OR nutrition supplementation in childhood) AND (adolescent OR adolescence OR adult OR adulthood) AND (longitudinal OR prospective OR cohort) " . The selection of studies was restricted to articles in humans. This resulted in 499 hits which were screened by reading the abstracts. A total of 39 studies met the inclusion criterion that the offspring body composition was assessed at the time of follow up. Fourteen among these were from developing countries and were selected for review. Additional manual search of the reference lists of the above articles was conducted and five more relevant studies were included.

We classified the selected studies into three categories based on the indicator used to assess the exposure of early nutrition: 1. Anthropometry (body size at birth and during early childhood): an indirect indicator of early nutrition; 2. Maternal nutritional intakes during pregnancy or 3. Biochemical indicators of nutrition estimated during pregnancy, both of which can be considered as direct indicators.

Observational studies relating low birth weight, childhood growth and later LBM

By far the largest body of evidence is available on the relationship between birth weight and later LBM as birth weight is a simple and commonly available proxy estimate of early nutrition. **Table 1** lists studies from India[26-29], Brazil [30-32], Korea [33], South Africa [34], the Philippines[35], and Guatemala[36,37]. In contrast to similar cohort studies from developed countries (e.g. the Hertfordshire cohort from the UK and the Helsinki birth cohort from Finland) where the body composition and chronic disease outcomes were assessed in middle-aged or elderly adults [38,39], the cohort members in these studies were younger (range = 4-32 years) at the time of the outcome assessment. As the body composition in childhood and adolescence tracks into adulthood, these studies provide insights on the association of birth weight with the adult LBM [40,41]. Moreover, the younger age of the cohort participants could be an advantage in the assessment of early influences on later body composition as this assessment is done before these relationships are substantially modified by adult lifestyles. However, pubertal assessment in some of the cohorts poses significant problems in interpretation of the findings as marked physiological changes in body composition take place during this dynamic phase of growth.

The relationship between early growth and later LBM observed in different studies varied depending on the age at assessment of the outcome measures. For example, studies where the outcome assessment was completed during pre-pubertal period (Pune [27] and Mysore cohorts [42] from India) showed a positive relationship of birth weight with LBM as

well as FM whereas studies with outcome assessment done during puberty (Korea [33] and South Africa [34]) showed a positive relationship of birth weight with FM only. However, cohorts where LBM was measured after completion of puberty (studies from Vellore and New Delhi, India [28,29], the Philippines [35] and Guatemala [36,37]) consistently showed a positive association between early growth and LBM at the time of follow up measurement. The association of early growth with LBM at a later age has also been highlighted by a recent study which reported an estimate with pooled data from five well characterized birth cohorts from low- and middle-income countries included in **Table 1.** [34] A number of explanations for these findings are possible. Puberty offers an opportunity for catch-up growth in height (which is closely linked to LBM) as indicated by studies which showed that under-nourished children tend to have delayed onset of puberty and also a prolonged pubertal development which allows at least partial catch-up in height. [43-45] It is possible that the catch-up in height is associated with catch-up in LBM as well. Therefore, the assessment of outcome before the substantial gain in lean and muscle mass achieved during puberty could explain the different findings at these two time points. Other reasons that could account for the differences observed in these studies may be related to different methods used for body composition assessment as well as the way child growth was modelled while analysing this relationship. For example, the study from the New Delhi birth cohort used the conditional SD scores of BMI change during different time periods in childhood in order to produce a measurement that is uncorrelated [28] whereas the study from The Philippines used the velocity of weight gain during different growth periods. [35]

Patterns of growth during different intervals of infancy and childhood are known to have distinct relationship with LBM and FM compartments during adult life. For example, the New Delhi Birth Cohort study which included growth measurements till 21 years of age showed that birth weight & BMI gain during first 2 years had stronger relationship with the

LBM in adulthood, BMI gain from 2 to 6 years was related to both FM and LBM whereas BMI gain during later childhood and adolescence was associated with FM at the time of follow up. [28] A smaller study based on the follow up of the Pelotas birth cohort from Brazil corroborated these findings. This study assessing the body composition by bioelectrical impedance assessment in 9 years old boys showed that weight gain during infancy was associated with LBM; weight gain during 1 to 4 years was associated with LBM as well as FM whereas weight gain after 4 years of age was associated with FM at the time of follow up assessment[32]. Studies from South Africa and Guatemala as well as the pooled data from five birth cohorts from the low- and middle-income countries also confirmed the association between growth during first 2 years of life and later LBM [34,36,37].

Although these patterns of association between early growth and later LBM revealed by the above observational studies cannot be considered as causal, long lasting impact of early nutrition on the LBM is plausible considering the developmental plasticity of muscle tissue. Muscle fibre number, a critical determinant of muscle mass, is set during gestation and animal studies have shown that prenatal maternal diet restriction is associated with reduced neonatal muscle weight which persists in later life [46,47].

Early growth in length and weight may have different implications for later body composition because of differences in the tissue accretion patterns[48]. However, no consistent relationship between the growth in length or weight in early life and the later LBM was observed in the studies reviewed here. For example, in studies from Mysore [42] and Pune [27] from India and Guatemala [36], association between early growth and later LBM or muscle mass was similar when assessed using increase in either length or weight as indicator of growth. On the other hand, studies from Brazil showed that although weight gain during infancy was positively associated with later LBM and FM, change in height during early years did not show any association with either LBM or FM at the time of follow up.[31,32]

Reasons for these differences are not clear and more studies assessing the tissue accretion patterns in relation to catch up growth in height and weight are required.

Sex differences in the association between early growth and later body composition have also been noted in some of these cohort studies. In general, the positive relationship between early growth and later LBM was stronger in males than in females of the cohort. For example, in the Pelotas cohort study from Brazil, rapid weight gain during infancy was positively associated with height and LBM at follow up in males, but less consistently so in females. [31] The authors speculated that this reflects contrasting tissue "investment strategies" in case of pubertal males and females. Similarly, in the New Delhi birth cohort study, early growth showed positive relationship with adult LBM in males and with LBM as well as FM during adulthood in case of females [28]. In the Filipino cohort, males with rapid growth during the first 6 months of life reached puberty earlier, had higher testosterone levels, were taller and muscular and had higher hand grip strength. [35] These relationships were not observed in females of the cohort. The authors attributed these findings to the developmental plasticity of the hypothalamic-pituitary-gonadal (HPG) axis which regulates the resource allocation in support of growth and maintenance of sexually dimorphic traits like muscle. [49] Early infancy is the critical period for the postnatal surge in testosterone and nutrition and weight gain during this critical period can have long-term effects on hormone regulation and physical development.

In summary, the above evidence suggests that larger birth weight and higher postnatal growth in first one to two years of life is associated with a higher LBM during later life and this association is stronger in case of males than females. The evidence is consistent across the settings despite significant variation in these settings in terms of prevalence of low birth weight and the childhood nutritional status. Programming of adult LBM by birth weight is

considered to be an important link explaining the association between higher birth weight and reduced cardiovascular risk even in high income populations. [50]

Studies assessing the relationship of indicators of maternal nutrition with the LBM of the offspring

The above-mentioned studies using birth weight or weight during childhood as a proxy for early nutritional status have been criticized suggesting that these measures may not be the most appropriate indicators of nutritional status. Birth size is affected by the interaction between environmental and genetic influences and some researchers have argued that despite being a convenient marker in epidemiological research, it does not adequately describe the phenotypic characteristics of a baby with regard to long-term health outcomes. [51] Several paths of foetal growth can achieve the same birth size and the effect of programming does not necessarily affect the size at birth. For instance, in long-term follow-up of a birth cohort exposed to Dutch famine, prevalence of coronary heart disease was higher in those exposed to famine in early gestation than in the non-exposed but this effect was independent of birth weight. [52] It has, therefore, been suggested that a more direct indicator of nutrition exposure during early life is desirable to assess the role of early nutrition in the programming of adult health and disease. A number of studies have explored these relationships using the opportunity provided by the maternal nutrition supplementation trials during pregnancy, although these studies were primarily conducted to evaluate these interventions for improving pregnancy and birth outcomes. To our knowledge, five such studies have been reported to date from developing countries: three have assessed the impact of protein energy supplementation whereas two studies have examined the role of maternal micronutrient supplementation on the offspring body composition **(Table2)**.

The INCAP study in Guatemala conducted during 1969-77 assessed the impact of a high energy high protein supplementation to pregnant women and their children to the age of

7 years on various child health outcomes. When the body composition of participants was assessed with anthropometry during adolescence, intervention was associated with a taller height and a higher LBM, especially in females. [53] This long-term impact of supplementation was largely explained by the effect of supplementation on body size at 3 years of age. The Gambian study, however, did not support the above findings. This study examined the body composition (using bio-electrical impedance (BIA)) of 1270 children in the age group of 11-17 years whose mothers had participated in a cluster-randomized trial of protein-energy supplementation during pregnancy. [54] The intervention group received supplementation during pregnancy (from 20 weeks of gestation until term) while the control group received the supplement in the postpartum period for 20 weeks. The supplementation was associated with a significantly higher birth weight in the intervention group but the weights of infants in the two groups at 3 months of age did not differ. The follow-up study showed that there were no differences in the LBM and FM of the adolescents in the two groups. The authors speculated that the supplement provided to the control women may have influenced the growth of their infants possibly by improving the breast milk quantity or quality. Alleviation of between-group differences in the infant weights at 3 months of age may have reduced the differences in the LBM at the time of follow up assessment. Apart from the above randomized controlled trials (RCTs), a study in India assessed the impact of a protein-energy supplement provided to pregnant women and children (as a part of a government funded nutrition supplementation programme -Integrated child development services or ICDS) on the body composition and cardiovascular risk factors in the offspring in adolescence. [55] The study examined a cohort of 1165 adolescents aged 13-18 years and found that despite their taller height, participants in the intervention group had a similar LBM and FM (assessed by anthropometry) as the controls. Although the design of the trial allowed realistic estimation of the long-term impact of a nutrition intervention provided through the government

programme, it is possible that the effective dose of supplement was too small due to possible sharing of the supplement with other family members as the consumption of the supplement was not supervised. In addition, timing of the supplementation may not have been optimal for the programming of muscle mass as the women tended to start collecting the supplements from the ICDS centre in the second half of pregnancy whereas muscle development starts early during embryogenesis. [56]

Apart from protein energy, deficiency of vitamins and minerals during critical stages of development affects the foetal development and may influence the later risk of chronic diseases through a number of pathways including hormonal changes in the mother and the foetus as well as epigenetic gene regulation.[57] For example, iron and zinc status may influence the activity of insulin-like growth factor-1 (IGF-1) and its receptors and thus impact foetal growth [58,59] which may have implications for the adult onset chronic diseases. Two follow-up studies of RCTs originally conducted to assess the role of maternal micronutrient supplementation on perinatal outcomes have been reported to date (**Table 2**). The Nepal study assessed the impact of 5 micronutrient supplements provided daily during pregnancy in more than 4000 women: folic acid, folic acid + iron, folic acid + iron + zinc, multiple micronutrients, or a control. All the supplements additionally contained vitamin A. When the offspring (n=3324) were examined at the age of 6-8 years, the results showed that maternal supplementation with folic acid + iron + zinc was associated with an increase in mean height, decrease in FM indices but not with arm muscle area. Other micronutrient formulations, on the other hand, were not associated with differences in body composition assessed using anthropometry. [60] Another study from Bangladesh included 4436 pregnant women randomised into six equally-sized groups: double-masked supplementation with capsules of either 30 mg Fe and 400 µg folic acid, or 60 mg Fe and 400 µg folic acid, or multiple micronutrient supplement (15 micronutrients), was combined with a randomised early

invitation (around 9 weeks) or a usual invitation (around 20 weeks) to start food supplementation (608 kcal 6 days per week). When the offspring body composition was examined at about 5.5 y of age with BIA (n=2290), there were no differences in the groups in relation to timing of the invitation to food supplementation and/or the multiple micronutrient supplementation. [61]

Considering the results of the above supplementation studies together, the evidence on the "programming" effect of maternal nutrition supplementation on the offspring LBM, assessed in the follow-up trials of protein energy supplementation appears inconsistent and weak. Scant evidence on the impact of maternal micronutrient supplementation on the offspring LBM did not indicate a beneficial effect.

Studies assessing the relationship between biochemical indicators of maternal nutritional status and the offspring LBM

Only two studies assessing this relationship have been reported from developing countries so far, both from India (**Table 2**). The Pune Maternal Nutrition Study assessed the maternal nutrient intakes and blood parameters at 28 weeks in more than 700 women and prospectively assessed the birth size and later body composition (using DXA) along with other cardiovascular risk factors in the offspring at the age of 6 y. Higher maternal erythrocyte folate concentrations at 28 weeks predicted higher offspring adiposity but none of the maternal nutritional variables were related to the LBM of the children. [62] Another study from Mysore assessed the relationship between maternal vitamin D status during pregnancy and the offspring muscle mass (by anthropometric estimation of arm muscle area (AMA)) at 5 and 9.5 y of age. [63] The results showed that, at both ages, children born to mothers with vitamin D deficiency had significantly smaller AMA in comparison with children born to mothers with normal vitamin D status. Thus, there is only limited evidence that maternal

294 micronutrient status indicated by some of the biochemical parameters may be related to the
295 body composition of the offspring.

296 As discussed earlier, different studies have chosen either indirect (i.e. birth weight) or
297 direct indicators (i.e. maternal nutritional intakes or biochemical indicators of maternal
298 nutrition) of early nutrition in order to assess the relationship of early nutrition with later
299 body composition. Relative merits of these two indicators are still debated as the birth weight
300 may be considered as a 'stable' indicator of early nutrition influenced by a number of genetic
301 and environmental factors (e.g. peri-conceptual nutrition status, socio-economic position,
302 intergenerational influences on the birth weight, etc.) whereas the direct indicator of maternal
303 dietary intakes may indicate a relatively short-term nutritional exposure. The overall evidence
304 suggests that the studies that have assessed the relationship of birth size and childhood
305 growth with body composition during adulthood, i.e. after completion of pubertal growth
306 have shown a consistent positive association with LBM. On the other hand, studies assessing
307 these relationships using direct indicators of maternal dietary intakes have failed to show any
308 consistent relationship.

309 **Link between early under nutrition and later adiposity: possible mechanisms**

310 High prevalence of childhood under nutrition and adult-onset adiposity-related
311 chronic diseases in the transitioning countries calls for an additional explanation as
312 environmental influences such as increased dietary intakes and decreased physical activity
313 cannot explain these two contrasting phenomena. Studies exploring the association between
314 the childhood under nutrition and later LBM reviewed above provide important insights
315 regarding the paradox of the "double burden" of the two forms of malnutrition in these
316 settings.

317 As discussed above, there is consistent evidence that higher birth weight and growth
318 during infancy programs a higher LBM in adulthood. Therefore, it is plausible that the low-

income settings with high rates of childhood under nutrition will have a higher proportion of adults with low LBM and this is indeed seen, especially in south Asian countries.[64,65] Lifestyle changes associated with nutrition transition, especially the excessive intake of processed foods and reduced energy expenditure, may enhance fat deposition. The impact of the obesogenic environment in the transitioning societies is likely to be greater in population groups that experienced nutritional insults in early life.[66]

Evidence suggests that the low LBM itself may predispose to fat accretion by influencing the energy balance. It is well recognized that synthesis and breakdown of muscle protein are principally responsible for the energy expenditure of resting muscle and poor muscle and LBM could have a significant effect on energy balance.[67] It has been estimated that a deficit of 10 kg in muscle mass translates to a conservation of ≈100 kcal/day in energy expenditure which in turn translates to accumulation of 4.7 kg FM/year. [68] It may therefore be argued that poor muscle mass could be an important reason for the high fat phenotype in this population.

In addition, a number of energy-sparing mechanisms take place in adults who were under-nourished and stunted in childhood. For example, a study from Brazil showed that nutritionally stunted children had impaired fat oxidation and preferential oxidation of carbohydrate as indicated by a higher respiratory quotient (RQ) in the fasting state and at 30-min after a meal. [69,70] As oxidation of 1 g of carbohydrate is equivalent to 4 KCal compared to 9 KCal with the oxidation of 1 g of fat, tendency to store fat is enhanced with this adaptation, especially in an environment where physical activity is low. [71] However, in a study from Guatemala [72], as well as in a recent study from Cameroon [73], mean RQ and weight-adjusted resting energy expenditure (REE) did not differ between stunted children and non-stunted children. In the Cameroon study, stunted children had lower physical activity measured using accelerometers which corroborates the findings of a few past studies. [74,75]

A number of studies have demonstrated that cortisol plays a key role in "programming" after intra-uterine under nutrition. [76] Under nutrition is a powerful stimulator of stress and can prompt an increased secretion of cortisol leading to an increase in the cortisol-to-insulin ratio to direct energy in the form of glucose to the brain. [77] This hormonal imbalance also leads to a reduction in key hormones responsible for growth, such as IGF-1and thyroid hormones, leading to impaired linear growth as well as lower energy expenditure. [78] An excess of cortisol is also associated with profound changes in intermediate metabolism, resulting in long-term changes in lipid metabolism and an increase in the concentration of tumour necrosis factor-alpha . [79] Recent evidence on epigenetic programming suggests that early under nutrition can influence phenotype by modulation of genes that control DNA methylation and by histone acetylation. [80] It thus appears that early under nutrition during the critical stages of development induces a cascade of adaptive processes with short-term survival benefits but these become maladaptive in the face of lifestyle changes associated with nutrition transition.

Nutritional influences affecting the LBM during life course

Apart from the role of early nutrition in 'programming' of the LBM as discussed above, evidence suggests that nutritional influences continue to exert significant impact on the LBM throughout life course. The following sections provide a brief appraisal of evidence on the role of nutrients consistently linked to muscle and LBM (proteins and micronutrients including zinc, calcium and vitamin D) during different life stages. Only a few studies from developing countries that have specifically assessed the muscle mass or LBM as an outcome have been reported. We have therefore included relevant evidence from developed countries which is potentially generalizable to low- and middle-income settings. A large number of studies assessing the impact of the above nutrients on the LBM at different life stages have

been reported and a comprehensive review of this evidence is beyond the scope of this article. This review is therefore illustrative rather than exhaustive.

Dietary protein

Dietary protein plays a central role in development and maintenance of muscle mass by increasing the muscle protein synthesis and inhibiting the muscle protein breakdown, thereby allowing net protein accretion. [81,82] Essential amino acids are especially important in promoting muscle protein synthesis and Leucine seems to be the most influential in initiating the molecular events associated with muscle protein synthesis. [83] Observational studies have shown that higher intake of protein, particularly milk-based protein, is associated with higher muscle mass during childhood, puberty and adulthood. [84-86] Although a large number of studies have demonstrated a a positive impact of protein or amino acid supplements on muscle protein synthesis in young as well as elderly individuals [87], these supplements have not shown a consistent beneficial effect on the muscle mass or strength. [88] A recent meta-analysis which pooled data from 22 randomized controlled trials that included 680 subjects showed that dietary protein supplementation increased LBM as well as muscle strength compared with a placebo after prolonged resistance-type exercise training in younger and older subjects. [89] However, it is difficult to delineate the independent effect of protein supplementation on the LBM due to synergistic effect of protein intake and resistance exercise. A number of factors including protein dose, protein source, timing of intake as well as age and health status of subjects modify the impact of protein on muscle and therefore direct comparison of studies using interventions with different protein and amino acid composition and heterogeneous participant characteristics is not possible. [90] A number of studies have also indicated an increase in muscle 'anabolic threshold' during ageing and therefore a higher protein intake may be necessary to overcome the muscle anabolic resistance in the elderly.[91]

A concern has been raised that high protein intake in early life may increase the long term risk of obesity as intake of high protein formulae in infancy was associated with higher weight for length z score and FM during childhood in a few European studies. [92,93] However, the association of higher protein intake with later adiposity has been observed mainly in children from the industrialized countries where dietary protein intakes are often 2–3 times higher than the requirement and commonly exceed 15% protein energy percentage. [94] On the other hand, protein intakes of under nourished children from developing countries are usually considerably lower and improvement in protein intake is usually associated with improved childhood growth. [95] Findings from the affluent settings therefore cannot be extrapolated to the low income settings. Moreover, follow up assessment of the INCAP study cohort in Guatemala showed that exposure to high protein supplement in early life did not increase the risk of obesity in adulthood. [96]

Micronutrients

Although a large number of studies have assessed the impact of micronutrient supplementation on growth of children in low-income settings, only a few studies have examined their role in LBM development during growth and in adulthood. There is some evidence on the role of zinc, calcium and vitamin D in lean tissue synthesis.

Zinc

Zinc is known to promote muscle protein synthesis and studies have shown that addition of zinc to the re-feeding regimen of children with protein energy malnutrition decreased the energy cost of growth, indicating enhanced muscle tissue synthesis. [97] A few studies in children and adolescents have also reported a positive impact of zinc supplementation on the muscle mass and LBM. For example, a randomized placebo controlled trial of zinc supplementation (30 or 50 mg) for 12 months in rural Zimbabwean

418 schoolchildren (n=144 boys and 169 girls, 11-17 y) showed a significant positive impact of
419 the supplement on weight gain and arm muscle area-for-age Z-score in the first 3 months of
420 supplementation. [98] This effect was, however, not seen during the last nine months of
421 supplementation. The authors speculated that other nutrients may have become growth-
422 limiting during the last nine months. In another study in Ugandan preschool children (n =
423 153), supplementation with 10 mg zinc sulphate for 6 mo improved arm muscle area and
424 weight gain. [99] These findings have been supported by a RCT of zinc supplementation in
425 Chilean preschool children [100] whereas another trial in Mexican children failed to show an
426 impact of zinc supplementation on growth or body composition.[101]

427 Calcium

428 Limited evidence on the role of calcium nutrition in the LBM development of
429 adolescents is available. A RCT in Chinese adolescents that examined the impact of three
430 doses of calcium carbonate supplement in 257 healthy adolescents (12-15 y) for 24 months,
431 showed that LBM in the medium and high dose groups (230 mg/d and 500 mg/d,
432 respectively) was significantly higher than that in the low dose group (85 mg/d) ($p<0.05$) in
433 case of males. There was, however, no effect of calcium supplementation on body
434 composition in females. [102] Similarly, another study from Cambridge, UK which enrolled 143
435 boys aged 16–18 y, showed that supplementation of calcium (1000 mg/day for 13 months)
436 resulted in a significant increase in height and LBM compared to a placebo. [103] However,
437 studies from Denmark, Finland and New Zealand which assessed the efficacy of calcium
438 supplementation for LBM accrual in adolescent girls, did not show any beneficial effect. [104-
439 106] A study in pre-pubertal children (8-10 years) from New Zealand which assessed the
440 efficacy of a high calcium dairy drink supplementation for 18 months did not find a positive
441 impact of the intervention on growth as well as LBM compared to controls.[107] A recent meta-

analysis which included 17 studies involving 2088 children did not show an effect of calcium supplementation on LBM. [108]

In general, these studies show that calcium supplementation had beneficial effect in adolescent boys but not in younger children or in adolescent girls. The age specific positive impact of calcium supplementation in adolescents could be related to their higher requirements and therefore the possibility of larger deficits in their diets compared to the requirements. Reasons for the sex-specific impact of calcium supplementation on body composition are not clear. In addition, the differences in results of various studies could be related to the differences in the baseline calcium intakes of the participants as well as the dose and duration of the supplement.

Vitamin D

The role of vitamin D on muscle function is supported by the evidence that vitamin D receptor (VDR) is expressed in human muscle tissue. [109] VDR activation may promote *de novo* protein synthesis in muscle.[110,111] However, a few studies assessing the impact of vitamin D supplementation in adolescents did not show consistent beneficial effect. In a study from Lebanon, vitamin D supplementation for one year in 10-17 year-old girls demonstrated a positive effect with either low (5 µg/day) or high (50 µg/day) doses of vitamin D_3 on LBM (approx. 4 kg or 9%, as measured by dual-energy X-ray absorptiometry) when compared to the control group. The effect was more pronounced in pre-menarcheal girls and surprisingly, a beneficial effect was even seen in the low-dose supplement group which did not show an increase in serum 25(OH)D levels. [112] On the other hand, in a randomized clinical trial in girls (12-13 y) from Manchester, UK, supplementation of vitamin D_2 over 12 months could not detect positive effects on muscle mass or function although the supplement increased the serum vitamin D levels. [113]

Role of animal source foods in development of LBM

Animal-source foods, particularly meat and dairy products, are rich sources of protein and micronutrients including zinc, iron, calcium, vitamin B12 etc. Moreover, the micronutrients in the animal source foods are more bioavailable compared to the plant source foods. In resource poor settings of developing countries, higher proportion of dietary energy is consumed as low-cost cereals (e.g. rice, maize, wheat, sorghum) or root crops such as cassava. Proportion of energy provided by animal source foods typically varies from 5-10% in low income countries compared to > 30% in industrialized countries [114]. Limited evidence suggests that addition of animal source foods to children's diet may improve their linear growth and LBM. For example, a study from Kenya examined the growth and muscle mass of 544 schoolchildren (median age 7.1 y) after 23 mo of supplementation with a meat, milk or energy supplement compared to a control group without a supplement. [115] The results showed that children in the meat group had significantly higher gain in mid-upper-arm muscle area than the other groups. To a lesser extent, children who received the milk or energy supplement also gained more mid-upper-arm muscle area than the controls. Another community based study from Malawi which examined the efficacy of dietary diversification by increased intake of ASF (especially whole dried fish with bones) in children in the age group of 30-90 months, showed that the intervention enhanced Z-scores for mid-upper-arm circumference and arm muscle area, although it did not impact weight or height gain. [116] In addition, substantial evidence exists that higher intake of milk is positively associated with linear growth and higher LBM in infancy, childhood and adolescence. [95] This growth promoting effect of milk can be attributed to its high quality protein, multiple micronutrients (vitamin B12, vitamin A, riboflavin, folate) as well as stimulation of growth factors. [117]

Importance of considering childhood nutrition and adult body composition as a continuum

Childhood under nutrition, commonly measured as prevalence of underweight, encompasses both stunting and wasting. Prevalence of underweight, however, usually shows a higher correlation with prevalence of stunting than wasting in low-income settings indicating that underweight indirectly describes the magnitude of linear growth faltering and stunting in young children. [118] Children living in low income homes consume diets with low amounts of animal source foods and are unable to meet requirements of nutrients (proteins, zinc, calcium, and vitamin D) that are critical for linear growth. [119,120] Evidence cited above suggests that these nutrients are also important for LBM development throughout life course and optimal body composition in adulthood. Promoting linear growth during childhood is considered to be an important step in the development of optimal body composition in adulthood.[121,122] Although the importance of these nutrients for linear growth during childhood has been known for many years, their ongoing role in the development of adult LBM and muscle mass is not well recognized. The body of evidence discussed above highlights the need to consider the problems of childhood under nutrition and low LBM during adulthood as dual manifestations of sub-optimal status of these important nutrients. Low LBM may promote adiposity due to energy sparing adaptive mechanisms discussed in the previous section. Poor diets with deficiency of these critical nutrients throughout the life course thus provide at least partial explanation for the double burden of childhood under nutrition and adult adiposity in transitioning countries.

Implications of the evidence and future research needs

The current double burden of two opposing forms of malnutrition poses enormous challenges for the nutrition policies of the developing countries in order to address the problems of underweight and overweight simultaneously. Understanding the childhood under

nutrition and adult over nutrition as a continuum rather than mutually exclusive problems is particularly useful in this regard. Evidence using the life course approach suggests that nutrition influences adult LBM through 'developmental programming' in early life as well as through its continued role during childhood and adolescent growth. Nutrients such as proteins, zinc, calcium, vitamin D are particularly important for linear growth during childhood as well as for improvement of muscle mass in later life. Promoting optimal intakes of these important nutrients throughout life course would therefore help mitigate the double burden of these two seemingly opposite forms of malnutrition. Strategies to enhance the intake of animal source foods in children from the low income households would be particularly important for improving their linear growth and LBM.

These measures would require a strong evidence base to support the necessary policy changes. Particularly, more studies are necessary to evaluate the efficacy and effectiveness of strategies to improve birth weight, linear growth in children and promotion of optimal body composition with higher LBM in adults in developing country settings. In addition, studies on feasibility and cost-effectiveness of these approaches in different settings are required as the effectiveness of these interventions is likely to be context-specific.

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Declaration of interest

Authors declare no conflict of interests.

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Legend for figure 1

Nutritional influences affecting the lean body mass during the life course

Footnote –

REE: Resting energy expenditure

Table 1 Studies from developing countries assessing the relationship of birth size and childhood growth measurements with body composition at a later age

No.	Country (city)	Measures at birth	Measures of childhood growth and frequency of measurement	Method of body composition assessment	N	Mean age at outcome assessment (y)	Relation between birth weight, childhood growth and later body composition	Reference
1	India (Pune)	Weight, length	Weight, height, MUAC, skinfold thickness measured every 6 mo	DXA Anthropometry	698	6	Birth weight as well as growth in height, weight and MUAC during follow up from birth to 6 y: related to LBM + and FM +	Joglekar CV, et al. (2007)[27]
2	India (New Delhi)	Weight, length	Weight and height measured : from birth to1 y – every 3 mo From 1y to 14 y – every 6 mo	Anthropometry	M 886 F 640	29.2	Birth weight and BMI gain from birth to 2 y: related to LBM+ in M and related to FM+ and LBM+ in F BMI gain during 2 to 6 y: related to LBM+ and FM+ in both M and F BMI gain in later childhood and adolescence: related to FM+ in both M and F	Sachdev HS, et al. (2005)[28]
3	India (Mysore)	Weight, length, MUAC	Weight and height measured annually from birth to 5 y and 6 monthly from 5 to 9.5 y	Anthropometry	M 275 F 299	9.5	Birth size (weight, height, MUAC) : related to AMA + Growth in height and weight during follow up: related to AMA +	Krishnaveni GV, et al. (2010)[26]
4	India (Vellore)	Weight	--	DXA	M: 61 LBW, 56 NBW	20	Birth weight : related to LBM +	Thomas N, et al. (2012)[29]
5	The Philippines (Cebu)	Weight	Weight measured every 6 mo from birth to 24 mo	Anthropometry	M 770	21	Birth weight and weight gain from birth to 12 mo: related to LBM+ and AMA +	Kuzawa CW, et al. (2010) [35]
6	Brazil (Pelotas)	Weight, length	Weight and length/height at 6 mo, 1 and 4 y	BIA	M 172	9	Birth weight: related to LBM+ Weight gain during 1to 4 y: related to LBM+ and FM+ Weight gain during 4 to 9 y: related to FM+ Change in height during follow up: not related to LBM or FM	Wells JC, et al. (2005) [32]

7	Brazil (Pelotas)	Weight, length	Weight and length/height at 6, 12 and 48 mo	Isotope dilution technique	M 222 F 203	14	Birth length : related to LBM in M and F Weight gain in infancy : related to LBM+ in M and FM+ in F Weight gain during 1 to 4 y : related to FM+ and LBM+ in M and F Change in height during follow up: not related to body composition	Wells JC, et al. (2012) [31]
8	Brazil (Pelotas)	Weight	HAZ, WAZ, WHZ at 2 & 4 y	BIA	M 2251	18	HAZ, WAZ, WHZ at 2 and 4 y : related to LBM + and FM+	Gigante DP, et al. (2007)[30]
9	South Africa	Weight	Weight at 12, 24 & 60 mo	DXA	M 160 F 142	15.5	Weight gain in first 2 y: related to LBM + (weak)	Kuzawa CW, et al. (2012)[34]
10	Guatemala	Weight, length	Weight and length at 15 days and 2 y in a sub-sample	Anthropometry	M 136 F 131	24	Birth weight, length at 15 days and length at 2 y : related to LBM in M & F	Li H et al. (2003)[37]
11	Guatemala	Weight, length	Weight and height at 1,3, 5 and 7 y in a sub-sample	Anthropometry	M 352 F 358	32.7	Weight and length at birth: related to LBM+, BMI gain in later childhood : related to FM+	Corvalan C, et al. (2007)[36]

M: males; F: females; LBM: Lean body mass; FM: Fat mass; AMA: Arm muscle area; DXA: Dual energy X-ray absorptiometry; BIA: Bioelectrical impedance; LBW: low birth weight; NBW: normal birth weight; SGA: small for gestational age

+ indicates positive relationship

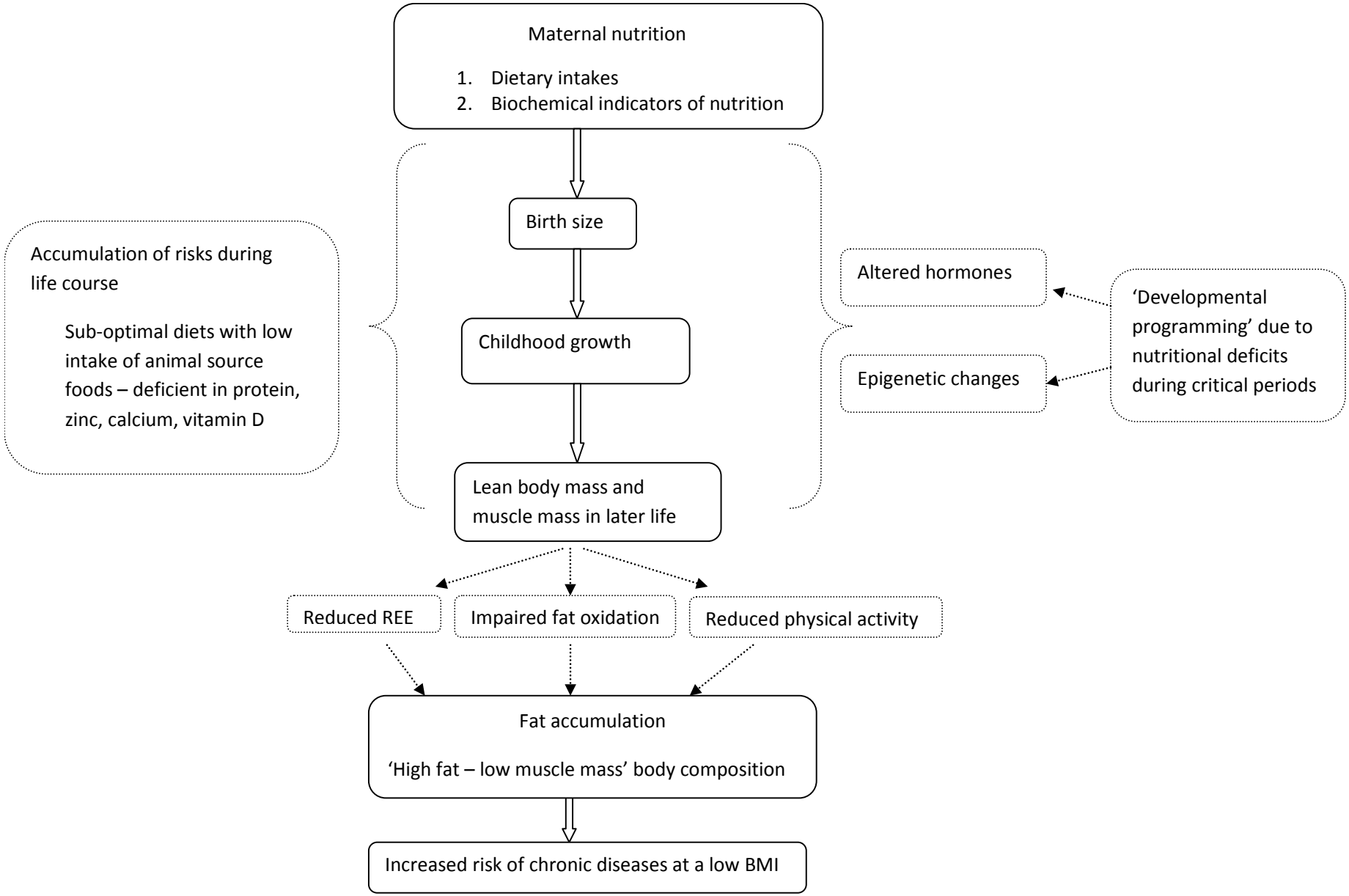
Table 2 Studies from developing countries assessing the relationship of early nutrition exposure with body composition at a later age

No.	Country (City)	Indicator of early nutrition exposure	Method of body composition assessment	N	Mean age (y)	Relation between early nutrition exposure &later body composition	Reference
1	India (Hyderabad)	Participation in a government funded food supplementation programme for pregnant women and children less than 6 y	Anthropometry	M 628 F 537	15.5	Supplementation was not associated with a higher LBM or FM	Kinra S, et al. (2008) [55]
2	Guatemala	RCT comparing a high protein- energy supplement (I) with a low energy no protein supplement (C) given to pregnant women and children less than 7 y	Anthropometry	M 245 F 215	16.5	Supplementation was related to LBM+ in girls during adolescence	Rivera JA, et al. (1995) [53]
3	Gambia	RCT comparing protein energy supplementation given to pregnant women (I) with that given in the postpartum period (C)	BIA	M 659 F 611	13.8	Maternal supplementation was not related to the body composition of adolescents	Hawkesworth S, et al. (2008)[54]
4	Nepal	RCT in pregnant women who were randomized to receive 1 of 5 micronutrient supplements: folic acid, folic acid + iron, folic acid + iron + zinc, multiple micronutrients, or a control. All supplements had additional Vitamin A.	Anthropometry	M 1601 F 1580	7.5	Maternal supplementation with folic acid + iron + zinc was related to increase in height and decrease FM indices but not related to AMA. Other micronutrient supplements were not related to body composition.	Stewart CP et al. (2009) [60]

5	Bangladesh	RCT of supplementation with capsules of either 30 mg Fe and 400 µg folic acid, or 60 mg Fe and 400 µg folic acid, or multiple micronutrients, combined with a randomized early invitation (around 9 weeks) or a usual invitation (around 20 weeks) to start food supplementation (608 kcal/day 6 days per week).	BIA	2290 (M and F)	4.5	No differences in LBM or FM in relation to the time of invitation to food supplementation or the micronutrient supplementation.	Khan, A. I., et al. (2012)[61]
6	India (Mysore)	Maternal serum vitamin D levels at 28-32 weeks of gestation.	Anthropometry	M 244 F 267	5 and 9.5	Maternal vitamin D deficiency – related to AMA + of the offspring at 5 and 9.5 y.	Krishnaveni, G. V., et al. (2011) [63]
7	India (Pune)	Maternal vitamin B12 and folate status at 28 weeks of gestation.	DXA	653 (M and F)	6	Higher maternal folate concentration- related to FM + Maternal vitamin B12 and folate status – not related to LBM.	Yajnik CS, et al (2008) [62]

LBM: Lean body mass; FM-Fat mass; AMA: Arm muscle area; DXA: Dual energy X-ray Absorptiometry; BIA: Bioelectrical impedance; RCT: Randomized controlled trial

+ indicates positive relationship


Maternal nutrition
1. Dietary intakes
2. Biochemical indicators of nutrition
Birth size
Childhood growth
Lean body mass and muscle mass in later life
Accumulation of risks during life course
Sub-optimal diets with low intake of animal source foods – deficient in protein, zinc, calcium, vitamin D
Altered hormones
Epigenetic changes
'Developmental programming' due to nutritional deficits during critical periods
Reduced REE
Impaired fat oxidation
Reduced physical activity
Fat accumulation
'High fat – low muscle mass' body composition
Increased risk of chronic diseases at a low BMI